Impact of 4-Dimensional CT (4D-CT) on Toxicity, Outcomes, and Dose Escalation for Radical Lung Cancer Radiation Therapy

of the histological types of non-SCLC, accounting for 1-3% of all SCLC. The low incidence has precluded the development of randomized clinical trials. To investigate the clinical features, prognostic factors, as well as the role of radiation therapy, we designed this retrospective analysis.

Materials/Methods: Between January 2004 and December 2011, patients with histologically diagnosed CSCLC in CIH-CAMS were retrospectively analyzed. The overall survival (OS), progression free survival (PFS), loco-regional recurrence free survival (LRFS), and distant metastasis survival (DMFS) were calculated by Kaplan-Meier method.

Results: Forty-four patients were enrolled, with a median age of 59 years old. The most common combined component was squamous cell carcinoma (59.1%). The disease of stage I, II, III and IV was 13.6%, 20.5%, 47.7% and 18.2%, respectively. Thirty-seven patients (84.1%) received multimodality treatment, including 37 (84.1%) with chemotherapy, 34 (77.2%) with surgery, and 23 (52.3%) with radiation therapy. The median follow-up was 24 months. The median time of OS, PFS and LRFS was 26.5-, 13.3-, 18.4-month, respectively. The 1-, 3- and 5-year OS was 68.6%, 46.9% and 32.8%, respectively, with corresponding PFS of 51%, 45.4% and 32.3%, and LRFS of 61.7%, 43.3% and 34.6%, respectively. The median DMFS of patients with stage I-III disease was 40.8 months, with 1-, 3- and 5-year DMFS of 59.5%, 51.5% and 36.6%, respectively. On univariate analysis, KPS 3 cm ($p = 0.049$), and positive margin ($p = 0.001$) were associated with lower OS. Radiation therapy significantly improved OS in patients with IIIA/IIIB disease ($p = 0.032$), positive lymph nodes ($p = 0.006$), trended to increase the OS in patients with T3-4 disease ($p = 0.179$), but not in those with different age, sex or tumor site. For patients who had received surgery, radiation therapy significantly improved OS only in patient with >4 metastatic lymph nodes ($p = 0.025$).

Conclusions: CSCLC is a rare type of SCLC with relative limited stage and good prognosis. KPS 3 cm and positive margin were poor prognostic factors. At present, multimodality therapy is recommended. Radiation therapy can benefit the patients with IIIA/IIIB CSCLC, or positive lymph nodes, or those with >4 metastatic lymph nodes after surgery.

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Impact of 4-Dimensional CT (4D-CT) on Toxicity, Outcomes, and Dose Escalation for Radical Lung Cancer Radiation Therapy

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Purpose/Objective(s): To investigate the dosimetric and potential clinical benefits predicted by using 4D-CT compared with 3D-CT in the planning of radical radiation therapy for non-small cell lung cancer (NSCLC).

Materials/Methods: Twenty consecutive patients suitable for radical radiation therapy were planned using free breathing 4D-CT. Retrospective delineation of the gross tumor volume (GTV) was performed on the helical scan set (3DCT). Beam arrangement and total dose (55 Gy/20 fractions) were matched for 3D versus 4D. Plans were compared for differences in planning treatment volume (PTV) geometrics and toxicities for organs at risk (OAR) using dose volume histograms (DVH). Tumor control probability and normal tissue control probability (TCP/NTCP) modeling was calculated using the Lyman-Kutcher-Burman (LKB) model and compared with a predictive clinical algorithm (Maastro), which in addition to dosimetry incorporates important patient characteristics such as: age, performance status (PS), smoking history, lung function, staging and concomitant chemotherapy to predict survival and toxicity outcomes. Differences between 3D and 4D plans were calculated using the Wilcoxon matched-pairs signed rank test, correlation between the clinical and mathematical model was calculated by the Spearman's rank correlation coefficient (r_s). Potential therapeutic gains between 3D and 4D were investigated by applying isotoxic dose escalation using constraints for mean lung dose (18 Gy), esophageal max (70 Gy) and spinal cord (48 Gy).

Results: The 4D plans had significantly lower PTV volumes ($p < 0.0001$) and reduction in toxicity to OARs ($p < 0.0015$) as well as lower predicted NTCP rates on LKB modeling ($p < 0.006$). The clinical algorithm did not exhibit any significant difference for dyspnea (grade ≥2) ($p > 0.999$) and 2 year survival rates ($p = 0.0831$) but did show a predicted difference for esophagitis (grade ≥3) ($p = 0.0132$) between 3D and 4D plans. There was no correlation between predictions from LKB modeling and the clinical algorithm for lung toxicity ($r_s = -0.36$, $p = 0.115$) or survival ($r_s = 0.342$, $p = 0.1399$), there was good correlation for predicted esophagitis ($r_s = 0.811$, $p < 0.001$). In 15/20 cases (75%), dose escalation of >1% was possible using the 4D plans compared to 3D, with a mean increase in dose by a factor of 1.19 (10.45 Gy).

Conclusions: The 4D-CT can lead to theoretical gains in therapeutic ratio based on DVH measurements and TCP/NTCP modeling; however when individual characteristics such as co-morbidity, lung function, age and PS are introduced this gain may be less evident in terms of survival and dyspnea rates. The 4D-CT allows potential for isotoxic dose escalation which may lead to improved local control rates and better overall survival in lung cancer by using personalized radiation therapy dose prescriptions.

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Thoracic-Only Extensive Stage Small Cell Lung Cancer: Assessment of the Benefit of Thoracic and Brain Radiation Therapy Using the SEER Database

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Purpose/Objective(s): Extensive-stage small cell lung cancer (ES-SCLC) includes patients with metastatic disease outside the thorax as well as those with locally advanced disease confined to the thorax without distant metastases. The latter group involves thoracic disease that cannot be encompassed in a practical radiation portal either due to an extremely large primary, contralateral lung parenchymal disease, pleural effusion or diffuse lung disease. Thoracic radiation therapy (TRT) and brain radiation therapy (BRT) have been used in patients with ES-SCLC after achieving a response to chemotherapy. This study aims to assess the benefits of TRT and/or BRT on overall survival (OS) in thorax confined ES-SCLC (T) in comparison to those benefits in the metastatic group (M) using a Surveillance, Epidemiology, and End Results (SEER) database analysis.

Materials/Methods: Demographic and staging data, identified from National Cancer Institute's SEER program, were available in 50,193 ES-SCLC pts, diagnosed between 1988 and 2009. TRT and BRT data were available for 10.191 pts treated between 1998-1997. The T ES-SCLC group included 1122 pts (11%). OS and CSS were estimated by the Kaplan-Meier method. OS hazard ratios (HR) for prognostic factors including patient age, gender, race, tumor size, grade, laterality, T and N stage, TRT, BRT and year of diagnosis were estimated using the Cox proportional hazards model.

Results: In the T group, TRT and BRT were delivered in 533/1122 and 69/1122, respectively. The 3 year OS was 6.6% vs 3% favoring the TRT vs no TRT group ($p \leq 0.001$). Patients who received BRT had 11.5% OS at 3 years vs 4.5% without BRT ($p < 0.001$). The multivariate analysis (MVA) of OS in the T group was significant for age at diagnosis >70 years with a hazard ratio (HR = 1.85, $p < 0.001$), TRT (HR = 0.7, $p \leq 0.001$) and BRT (HR = 0.7, $p = 0.0078$). In the metastatic group (M), 3065/9069 received TRT while 1908/9069 received BRT. The 3 year OS was 2.4% vs 1.1%, favoring the TRT vs no TRT group ($p \leq 0.001$). BRT had 2.1% OS at 3 years vs 1.4% ($p \leq 0.001$) in the no BRT group. Similar to the T